REMARKS/ARGUMENTS

Reconsideration of the above-identified application is respectfully requested.

Summary of the Invention

The present invention is based on the discovery that the treatment of a cancer is enhanced by using combinations of a telomere damaging agent, such as paclitaxel, with an agent that inhibits telomerase, thereby reducing telomerase activity that leads to resistance to paclitaxel treatment. Applicants discovered that other cytotoxic treatments, such as, for example, cisplatin, radiation, hyperthermia, and serum starvation, also induce telomerase activity. Applicants discovered that combining paclitaxel with a telomerase inhibitory agent, such as 3'-azido-deoxythymidine (AZT) or 2', 3'-didehydro-3'deoxythymidine (d4T), results in a synergistic improvement in effectiveness of paclitaxel for treating cancers. These discoveries have led to the present invention. Applicants have further discovered that the AZT doses indicated to enhance the antitumor activity of paclitaxel are about 20-fold lower than the AZT doses used in the prior art. Similarly, the AZT concentrations needed to enhance the paclitaxel activity are at least several folds lower than the AZT concentrations shown in the prior art needed to produce 50% inhibition of telomerase activity. Applicants further defined the AZT and d4T concentrations and the AZT doses that produce the greatest synergy with paclitaxel, whereas the prior art does not provide such enabling steps.

Claim Amendments

Claim 1 has been amended to explicitly claim classes of telomere damage-inducing agents of the invention that are disclosed in the Application. (See p. 13, ll. 27-33) While the application discloses a large number of other agents and types of agents which possess either telomere damage-inducing activity and/or telomerase inhibitory activity, the application has previously been subject to a restriction requirement. The scope of claim 1 is such that claim 1 specifically claims those telomere damage-inducing agents that are both disclosed in the Application and that the Applicants have documented possess the telomere damage-inducing activity claimed. The submitted Declaration provides further documentation that the Applicants possess the invention as disclosed in the Application and as claimed. Those skilled in the art will recognize without undue experimentation that other agents from the groups disclosed by Applicants are equivalent to those described in the Application and the Declaration. New dependent claims 93-96 claim individual groups of agents within the scope of claim 1,

Amended claim 42 and new claim 97 reflect similar language to that found in claim 1, but with slightly different scope. Claim 97 claims a different scope of the groups of telomere damage-inducing agents, and largely replaces the scope of previously examined claim 2. Where claims 1 and 97 are drawn to a method for inhibiting or reducing the growth of a cell, claim 42 is directed to a method of treating cancer. New dependent claims 98-126 are of similar scope to the claims depending on claim 1, which have been previously examined.

Claims 33 and 34 has been amended in the preamble to provide a reference to the Applicants' invention of a method for screening agents that are effective for inhibiting growth of a cell. Claim 34 has also been amended to reflect the same scope as claim 1 when utilized in a screening method. The applicants' invention of a method of screening an agent is disclosed in the Application beginning at p. 23, l. 10 and continuing through p. 25, l. 6. Applicants have amended claims 33 and 34 to include a reference to an aberrant cell to clarify the claimed invention. This amendment does not narrow the claims, and is not in response to any rejection. The term aberrant in relation to cellular growth behavior is supported in the application at p. 3, l.13, p. 13, l. 15, and in the Definitions at p. 9, ll. 20-22. The amendments to claims 33 and 34 do not broaden the scope of the claims in anyway, and have been submitted primarily to assist in pointing out what is claimed.

Claims 3-5, 9-14, 16, 18, 20, 22-24, 28, 44, and 45 have been amended to eliminate multiple dependent claims from the application. Claims 40 and 41 have been canceled to simplify the Examiner's consideration of Claim 42. Claims 91 and 92 were objected to based on the presence of informalities. Claims 91 and 92 have been amended to correct typographical errors. No admission regarding patentability should be presumed or inferred from these amendments and cancellations.

No new matter is added by virtue of these claim amendments. Applicants assert that no claims have been narrowed with the meaning of *Festo* (*Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 US 722, 112 S.Ct. 1831, 152 L.Ed.2d 944, 62 USPQ2d 1705 (2002)). See also *Interactive Pictures Corp. v. Infinite Pictures Inc.*, Fed Cir., No. 01-1029, December 20, 2001 (addition of the words "transform calculation" was not a narrowing amendment because that addition did nothing more than make express what had been implicit in the claim as originally worded).

Because the Applicants remaining arguments are based on legal grounds and on a Declaration from one of the Applicants, the remaining claims have not been amended. Several of the previously withdrawn claims are now cancelled in order to put the application in condition for allowance.

Claim Rejections

Amendments in response to Examiner's interview.

In a telephone interview, Examiner kindly drew Applicants' attention to potential problems with claim indefiniteness that had not been the subject of any rejection. In order to advance prosecution and place the Application in form for allowance or appeal, Applicants have amended claim 1; canceled claim 2 and replaced it with claim 97; and amended claims 33, 34, and 42. To assist the Examiner's consideration of the Application, claims 1, 33, 34, and 42 now list functional groups of telomere damage-inducing agents.

There is support in the application for listing these particular groups. (See p. 13, ll. 27-33) One of the inventors, Dr. Au, submits herewith an Declaration that specifically points out the Applicants' possession of the invention and support for the premise that compounds from the functional groups of the amended claims can be identified without undue experimentation. Applicants have not amended claims 1, 33, 34, or 42 to list specific telomerase inhibitory agents, as such agents are not only well-known in the art (see p. 20, l.14-p. 23, l. 8), but also are disclosed in the Application, and can be identified without undue experimentation. (See Au Declaration, paragraphs 6, 7).

Applicants therefore respectfully request that the Examiner withdraw his objections and allow the amended claims, or enter the claims to place the application in proper form for appeal.

102 (b) Claim Rejections Based on Gill.

Claims 1-4, 8-10, 12-14, 16, 18, 20, 22-24, 26, 33-35 and 40-46 stand rejected under 35 U.S.C. §102(b) as being anticipated by Gill (U.S. Patent No. 5,756,537). Gill teaches that paclitaxel can be administered concurrently with AZT for the treatment of Kaposi's Sarcoma in patients with acquired immunodeficiency syndrome (AIDS).

This prior art in fact teaches that paclitaxel can be used to treat Kaposi's Sarcoma in AIDS patients who routinely received AZT and other reverse transcriptase inhibitors to manage the AIDS, but does not teach that adding AZT, d4T, or other reverse transcriptase inhibitors, through inhibition of telomerase, enhance the antitumor activity of paclitaxel. The art use of paclitaxel in combination with telomerase inhibitors is simply a coincidence of treating two distinctly different diseases, and does not enable an improved treatment of cancer. Hence, in the absence of the present invention, there is no motivation to use AZT, d4T or other reverse transcriptase inhibitors to enhance the telomere-directed effect of paclitaxel.

The disclosure of Gill shows no evidence of improved therapeutic response to the combination of AZT and paclitaxel, and in fact does not differentiate between Kaposi's sarcoma patients receiving AZT and those that are not. It is not possible for the artisan to infer from Gill that the combination of AZT with paclitaxel will lead to improved treatment of Kaposi's sarcoma in patients not infected with HIV, let alone improved treatment for the plethora of other, more common, cancers. Prior to the Applicants' invention, use of AZT by patients not infected by HIV was generally contraindicated. Considering the side effects of AZT, it would have violated accepted medical principles to administer AZT to patients not being treated for retroviral disorders. The Examiner admits that "Gill does not teach any synergistic benefit using the combination" (page 7). Even in Example 6, cited by the Examiner, only 16% of the participating patients were receiving AZT. Applicants do not attempt to claim all medical treatments that combine AZT with paclitaxel. Gill, nonetheless, offers no motivation at all for a practitioner to combine paclitaxel with AZT. Applicants' invention is the combination of a telomere damaging agent, such as paclitaxel with a telemorase inhibitor, such as AZT or d4T.

Furthermore, the present invention enables the identification of an AZT treatment schedule to enhance the efficacy of paclitaxel, which cannot be found in the prior art, as the prior art does not provide guidance to finding such a treatment schedule. For example, the doses of AZT required for treatment of AIDS are 20 fold higher compared to the AZT doses required to enhance the paclitaxel effect. The intravenous AZT dose of 5-6 mg/kg/day used to treat AIDS (PDR electronic library. Online version. Under Retrovir®). Example 9 shows that the intravenous AZT dose required to enhance the survival advantage of paclitaxel in tumor-bearing mice is approximately 0.24 mg/kg/day. Claims 26, 91, and 92 reflect the AZT doses and the ratios of AZT: paclitaxel concentrations discovered by the present invention.

The law is clear that an unrecognized occurrence does not anticipate Applicants' invention. Gill does not recognize that combining a telomere damaging agent, such as paclitaxel, with a telemorase inhibitor, such as AZT or d4T, will lead to enhanced treatment effectiveness. The combination of paclitaxel with AZT is simply not inherent in the treatment practiced by Gill. "Inherency cannot be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances [such as combining paclitaxel with AZT] is not sufficient." Ex parte Skinner 2 USPQ 2d 1788, 1789 (BPAI, 1987). That a patient with AIDS may be given both paclitaxel and AZT does not anticipate all combinations of AZT with paclitaxel for cancer treatment because there is no motivation to combine these drugs, and the combination is not inherent in cancer treatment.

§ 103(a) Rejection Based on Gill in view of Merck Index

Claims 1-4, 7-28, 40, 42, and 44-47 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Gill, in view of the Merck Index. Gill teaches that paclitaxel can be administered concurrently with AZT to treat Kaposi sarcoma in AIDS patients, and that paclitaxel can be used with other antiretroviral agents that are used to treat AIDS. The Merck Index teaches that d4T is a reverse transcriptase inhibitor.

As discussed above, Gill does not teach using AZT to enhance the antitumor activity of paclitaxel and, therefore, does not teach how to find an AZT dose that can synergize with paclitaxel. In fact, Gill does not teach that any dose of AZT can synergize with paclitaxel. Hence, Gill does not render claims 1-4, 7-28, 33-35, and 40-47 unpatentable. The d4T doses used in AIDS patients are 60-80 mg per day (PDR electronic library. Online version. Under Zerit®). These doses would yield a maximum plasma concentration of about 4 micromolar (PDR electron library. Online version. Under Zerit®). The present invention teaches the synergy between paclitaxel and d4T where the d4T concentrations are at least 20 micromolar (see Example 8). This concentration is at least 5-fold higher compared to the concentration used to treat AIDS patients. Claims 26 and 27 were previously amended, indicating these teachings, as do previously added claims and claims 90-92 reflecting the distinguishing features of the present invention, regarding the AZT doses and concentrations and the d4T concentrations.

§ 112(a) (First Paragraph) Rejection for nucleoside analogs other than AZT and d4T

Claims 1-24, 28, 33-35, and 40-45 stand rejected to under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably provide enablement for treating cancer using paclitaxel and any nucleoside analog other than AZT or d4T. The Examiner cites reasoning of unpredictability in the art and the necessity of undue experimentation. Initially, Applicants would remind the Examiner that working examples in the above-identified application include guidance for choosing nucleoside analogs, and the art cited by the Examiner teachs the skilled artisan how to identify those analogs with inhibitory properties. Applicants submit herewith an Declaration from one of the inventors, Dr. Au, that states, in part, that one skilled in the art can determine without undue experimentation which analogs possess inhibitory ability. (See Au Declaration, Pararaph 6) Furthermore, the application discloses extensive prior art to guide the artisan in choosing telomerase inhibitory agents (See p. 20, l. 14–p. 23 l. 8; Table 1) so that no undue experimentation is required to practice the invention. Thus, withdrawal of the §112 rejection respectfully is requested.

The Examiner states that not all nucleoside or nucleotide analogues are polymerase inhibitors (e.g., reverse transcriptase). Nucleotide analogs are referenced in the application, wherein it is stated, *inter alia*:

> The term "nucleotide analog, or derivative thereof" refers to those art recognized modified nucleic acid bases that, typically, resemble a natural building block of DNA or RNA polymerization but have been modified to have an additional property such as, *e.g.*, the ability to inhibit a reverse transcriptase, *e.g.*, retroviral reverse transcriptases and telomerases.
>
> Application at page 11, ll. 32-36.

The definition of nucleoside analog certainly militates against the term being indefinite. Additional definitions of other analogs or derivatives and many other terms used in the application and claims are set forth in the definition section of the application at pp. 9-13.

Even though all nucleoside analogs are not inhibitors of polymerases, no undue experimentation is required to identify appropriate inhibitors. Any experimentation would be routine. See Pai et al., Cancer Research, 58: 1909-1913 (1998), Strahl, et al., Molec. Cell. Biol. 16: 53-56 (1996). "That some experimentation is necessary does not preclude enablement....It is not a function of the claims to exclude possible inoperative substances..." Atlas Powder Co. v. E.I. Du Pont de Nemours , 750 F.2d 1569, 1576, 224 U.S.P.Q. 409, 413 (Fed. Cir. 1984). Dr. Au's affidavit states that those skilled in the art of molecular biology have the readily available means, either through literature review, or through a simple test, to identify which of the universe of nucleoside analogs possess the ability to inhibit reverse transcriptase. The application describes exemplary tests that demonstrates the synergy between paclitaxel and two nucleoside analogs, AZT, and d4T with reverse transcriptase inhibitory activity. Even though the testing method "might be 'tedious and laborious,' such experimentation is nevertheless routine'." Johns Hopkins Univ. v. Cellpro, 931 F. Supp. 303, 322 (D. Del. 1996) aff'd in part, 152 F.3d 1342 (Fed. Cir 1998). "Routine experimentation may involve rather extensive studies without straying [into] undue experimentation." Ex parte D, 27 USPQ2d 1067, 1069-70 (BPAI 1993). There exists no requirement under §112 for the Applicants to test each and every possible nucleoside analog for the ability to inhibit reverse transcriptase in order for the Applicants to claim other unnamed nucleoside analogs.

The law, the disclosed data, Dr. Au's expert opinion, and the definitions in the application counter this claim rejection. Thus, its withdrawal respectfully is requested.

Previous § 103(a) Rejection Based on Vande Woude in view of Merck Index

In the most recent Office Action, the Examiner withdrew a rejection of claims 1-24, 26-28, 40-47 under 35 U.S.C. § 103(a) as being unpatentable over the Vande Woude (U.S. Patent No. 6,150,398), in view of The Merck Index, 1996, 7117,8958 and 1052. Nonetheless, the Examiner discussed Vande Woude. Applicants acknowledge the Examiner's statement that Applicants have overcome any rejection based on Vande Woude, and direct the Examiner's attention to the arguments against obviousness above regarding Gill. Because there is no outstanding rejection, no additional response by the Applicants regarding Vande Woude is required. Applicant rely on the Examiner's reassurance that there exists no standing rejection based on Vande Woude.

Conclusion

In view of the amendments and remarks submitted herewith, allowance of the claims and passage to issue of this application respectfully are requested.

Respectfully submitted,

Date: 23 December '03

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Appln. No. 09/587,662
Declaration dated December 23, 2003
Reply to Office Action of July 7, 2003

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	Jessie L.S. Au, *et al.*
Serial No.	:	09/587,662
Filed:	:	June 5, 2000
For:	:	METHODS AND COMPOSITION FOR MODULATING DRUG ACTIVITY THROUGH TELOMERE DAMAGE
TC/AU	:	1623
Examiner	:	Patrick Lewis
Attorney Docket No.	:	TNI 2-006

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DECLARATION UNDER 37 C.F.R. § 1.132

Declarant, Jessie L.-S. Au, does declare and state that:

1. She received her Doctor of Pharmacy and Doctor of Philosophy degrees from the University of California San Francisco, in 1972 and 1980, respectively. She has been on the faculty of The Ohio State University since 1983, rising to the rank of Full Professor in 1992. She has served on multiple government advisory boards (including, *inter alia*, Experimental Therapeutic Study Section, Pharmacology Study Section and Board of Scientific Counselors of the National Institutes of Health, U.S. Army Breast Cancer Program, and Cancer Center Support Grant Review Committee, Manpower Initial Review and Scientific Review Group (Subcommittee D) of the National Cancer Institute). She currently serves on the Developmental Therapeutics Review Committee for the National Cancer Institute. She is also on the Editorial Boards of *Pharmaceutical Research* and *PharmSci*. She received a Research Career Development Award and a Merit Award from the National Cancer Institute, and a Distinguished Scholar Award, the Dorothy M. Davis Chair in Cancer Research, and a Distinguished University Professorship from The Ohio State University. She is a Fellow of the American Association of Advancement of Science and a Fellow of the American Association of Pharmaceutical Scientists. She was Co-director of three research programs (Developmental Therapeutics, Urologic Oncology, Head and Neck Oncology), Director

of Translational Research, and Deputy Director of The Ohio State University Comprehensive Cancer Center, one of the then 28 centers in the U.S. that received such designation from the National Cancer Institute.

2. Her research interests and experience are to develop effective cancer chemotherapy, by identifying effective drugs or combinations of drugs, and by identifying the optimal treatment schedules including the dose and treatment duration. Her work in this area has led to the identification of a new treatment for bladder cancer, for which she has received U.S. Patent No. 6,286,513 B1. This new bladder cancer treatment is based on a new treatment schedule using mitomycin C, a drug that has been used for over 25 years. She and her co-inventor discovered that the prior regimen of administering mitomycin C was less than optimal and subsequently found a new treatment regimen that is nearly twice as effective in human patients, as compared to the prior regimen. She has further determined that suramin, an agent previously used to treat parasitic infections and known to counter growth factor action, enhances the efficacy of cancer chemotherapy when used in low doses. This new therapy, for which she has received U.S. Patent No. 6,599,912 B1, is currently in clinical testing.

3. Similarly, the above-identified patent application teaches a novel method to use existing drugs in a new way.

4. She is an inventor of and co-applicant for the above-identified application.

5. She and her co-inventor have determined that the combined application of a telomere-damaging agent and an inhibitor of telomerase, results in greater antitumor effect compared to either single agent. A telomere damage-inducing agent is defined in the application, and is an agent causing a measurable change to the end of a telomere, for example telomere shortening. Telomere shortening can be identified using the Telomere Amount and Length Assay (TALA) described in the application. See Table 1. Shortening of the telomere length as a result of chemotherapy was, for example, determined in FaDu cells, treated with a number of common chemotherapeutic agents. FaDu cells were cultured in minimal essential medium (MEM) supplemented with 9% heat-inactivated fetal bovine serum, 2 mM to L-glutamine and antibiotics at 37° C in a humidified atmosphere of 5% CO_2 in air. Representative agents from four major classes of anticancer drugs, including antimicrotubules, DNA alkylators, topoisomerase inhibitors and antimetabolites, were tested. Drug concentrations that produced 80% or greater cytotoxicity at 96 hours, as measur d by the sulforhodamine B assay, were used. The concentrations w re as follows: 100 nM for vincristine and mitoxantrone, 200

nM for docetaxel and paclitaxel, 250 nM for doxorubicin, 1 μM for methotrexate, and 100 μM for 5-fluorouracil. The telomere length was determined after 24 hours of drug exposure and compared with the length in control cells that did not receive drug treatment. It is noted that drug treatment resulted in detached cells whereas untreated control cells remained attached. The results are expressed as percentages of the untreated control cells at the beginning of the experiment or 0 hour. The eight compounds represented in the table below showed a shortening of the telomeres after 24 hours of drug exposure, and are, therefore, telomere damage-inducing agents. The data shown in Table 1 was determined after the Application was filed, using the methods disclosed in the Application as filed. All of the compounds listed in the table below were disclosed in the specification as potential telomere damage-inducing agents. (See p. 18, l. 24 – p. 19, l.12) The data below provides further exemplary support for the applicant's reduction to practice of the invention disclosed in the application.

6. The application discloses that the synergistic effects occur with two different nucleoside analogs, AZT and d4T. These nucleoside analogs act as reverse transcriptase inhibitors, and thus inhibit telomerase. Hence, the present invention is expected to be applicable to other nucleoside analogs that inhibit reverse transcriptase. Simple and routine laboratory tests are widely available to determine if a nucleoside analog is a reverse transcriptase inhibitor, and to determine if a compound is a telomerase inhibitor. Inhibition of reverse transcriptase action is frequently performed as described by Boyer, et al., Proc Natl Acad Sci USA 91:4882-4886 (1994), or by using a commercially available kit such as the RT SPA Enzyme Assay Kit sold by Amersham Life Science, Inc. (Arlington Heights, IL 60005). Inhibition of telomerase activity can be determined by the widely available, and routine "TRAP assay," as described in the application.

7. Based on this data and published reports in this field, it is her expert opinion that the invention disclosed along with the extensive existing art teaches the skilled artisan how to identify those nucleoside analogs that possess the ability to inhibit reverse transcriptase, and that only routine experimentation is necessary to practice the invention with other reverse transcriptase inhibitors.

8. Based on this data and published reports in this field, it is her expert opinion that the invention disclosed teaches the skilled artisan which compositions are effective as telomere damage-inducing agents and as telomerase inhibitory agents, and that no undue experimentation is necessary to practice the invention with other telomerase inhibitory agents.

TABLE 1

Effect on Telomere Length of Telomere Damaging Agents

Class of chemotherapeutic agents	Chemotherapeutic agent (Example No.)	Sample	Telomere length at 24 hours % of control at 0 hour
Antimicrotubule	Paclitaxel (Example 3)	Control	101.0
		Treated	66.4
	Docetaxel	Control	100.0
		Treated	63.6
	Vincristine	Control	101.6
		Treated	61.8
DNA alkylator	Cisplatin (Example 5)	Control	99.9
		Treated	85.4
Topoisomerase inhibitor	Doxorubicin	Control	101.4
		Treated	91.2
	Mitoxantrone	Control	102.1
		Treated	90.5
Antimetabolite	Methotrexate	Control	101.0
		Treated	86.1
	5-Fluorouracil	Control	99.6
		Treated	88.6

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Declaration dated December 23, 2003
Reply to Office Action of July 7, 2003

9. All statements made herein of her own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

FURTHER DECLARANT SAYETH NAUGHT.

Date December 23, 2003

Jessie L.-S. Au